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(54) Title: NOVEL AMINO-AZA-CYCLOHEXANES

(57) Abstract: The invention relates to novel compounds which are substituted amino-aza-cyclohexane derivatives of the general formula I. The invention also concerns related aspects including pharmaceutical compositions containing one or more compounds of the general formula I and their use as medicaments for the treatment of protozoal infections, especially malaria.



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## NOVEL AMINO-AZA-CYCLOHEXANES

5

The invention relates to novel compounds which are substituted amino-aza-cyclohexane derivatives of the general formula I. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of the general  
10 formula I and especially their use as medicaments to treat or prevent malaria infections or to treat or prevent other protozoal diseases like sleeping sickness, Chagas disease, amebiasis, giardiasis, trichomoniasis, toxoplasmosis, leishmaniasis etc.

### 15 ***Background of the invention:***

Numerous serious diseases affecting humans as well as domestic and livestock animals are caused by protozoal organisms such as Kinetoplastida, Apicomplexa, Anaerobic protozoa, Microsporidia and Plasmodium, for example. The best known of these diseases is malaria.

20 Malaria is one of the most serious and complex health problems affecting humanity in the 21<sup>st</sup> century. The disease affects about 300 million people worldwide [2], killing 1 to 1.5 million people every year. Malaria is an infectious disease caused by four species of the protozoan parasite Plasmodium, P. falciparum being the most severe of the four. All attempts to develop vaccines  
25 against P. falciparum have failed so far. Therefore, therapies and preventive measures against malaria are confined to drugs. Various classes of antimalarial drugs exist. The most widely used are the quinoline derived compounds, e.g. chloroquine which has been an especially effective drug for both prophylaxis and therapy. However, resistance to many of the currently available antimalarial  
30 drugs is spreading rapidly, threatening people in areas where malaria is endemic, and new drugs are needed. Reports of multi-drug resistant strains of malaria parasites render the search for new antimalarial agents especially urgent.

*P. Falciparum* enters the human body by way of bites of the female anophelino mosquito (it may also be transmitted by blood transfusion from asymptotic donors; almost all infected blood components including red cells, platelet concentrates, white cells, cryoprecipitates and fresh plasma can transmit malaria). The plasmodium parasite initially populates the liver, and during later stages of the infectious cycle reproduces in red blood cells. During this stage, the parasite degrades hemoglobin and uses the degradation products as nutrients for growth [1]. The limitations of the current antiprotozoal chemotherapeutic arsenal underscore the need for new drugs in this therapeutic area. The present invention relates to the identification of novel low molecular weight, non-peptidic, non-quinoline compounds which are able to kill the malaria parasite plasmodium falciparum to treat and/or prevent malaria.

The present invention provides an array of novel compounds. In preferred embodiments, these compounds may act as inhibitors of protozoal enzymes and are useful pharmaceutical agents for the treatment and prevention of protozoal infections. However, the mode of action could be unrelated to enzyme inhibition. For clarity and simplicity reasons, the following description is principally focused on compounds of the invention that inhibit enzymes relevant to the organism *Plasmodium falciparum*, the causative agent of malaria. This focus is intended to be illustrative and not limiting. Those skilled in the art will recognize a substantial structural homology and substrate specificity and activity overlap between the enzymes of *P. Falciparum* and other protozoa. Therefore, the compounds described in the invention are applicable for treatment or prevention of diseases caused by a variety of protozoa.

***Plasmodium falciparum* in vitro assay (<sup>3</sup>H-hypoxanthine incorporation):**

*Standard parasite strain:* *Plasmodium falciparum*, K1 (chloroquine and pyrimethamine resistant).

*Standard Drug:* Artemisinin (Arteannum, Quinghaosu; Sigma 36,159-3)

*Standard Conditions:*

Medium: RPMI 1640 without hypoxanthine supplemented with HEPES (5.94g/l),  
NaHCO<sub>3</sub> (2.1g/l), Neomycin (100U/ml) + Albumax<sup>R</sup> (5g/l), washed human red  
5 cells A+

Plates: Costar<sup>TM</sup> 96-well microtiter plates

Incubation: 37°C; 4% CO<sub>2</sub>, 3% O<sub>2</sub>, 93% N<sub>2</sub>.

*Drug Preparation:*

- 10 For the assay, the compounds are diluted from the stock solution in DMSO. The highest concentration is 2 mM, followed by six dilution steps with a dilution factor of 3.

*Assay Procedure:*

- 15 - prepare smears of the stocks of the plasmodium falciparum strains and determine the parasitaemia. The starting conditions for the assay are as follows:

concentration of red cells:	2.5% (v/v)
initial parasitaemia:	0.3%

20

- 1 µl of the compounds in DMSO is added to 200 µl of human red blood cells infected with parasite in complete medium. The compounds are tested in monoplicate and the concentration ranges from 10 µM to 10 nM. Six drugs can be tested this way on each plate. For each assay chloroquine and artemisinin  
25 are tested as the standards with 200 ng/ml as the highest concentration.

Compounds are tested in two independent assays and results are expressed in mean IC<sub>50</sub> values from the two experiments.

Scheme 1:

	1	2	3	4	5	6	7	8	9	10	11	12
A	positive control								negative control			
B	compound No. 1		compound No. 2		compound No. 3		compound No. 4		compound No. 5		compound No. 6	
C												
D												
E												
F												
G												
H												

A1 – A8: positive control, red cells and parasites

5 A9 – A12: negative control, red cells only (no parasites)

B1 – H12: serial drug dilutions for 6 compounds in duplicate

- The plates are incubated in an incubation chamber at 37°C in a humidified atmosphere containing the special gas mixture.
- 10 - After 48 hours 50µl <sup>3</sup>H-hypoxanthine (=0.5 µCi) are added to each well of the plate. The plates are incubated for another 24 hours.
- Then the plates are harvested with a Betaplate™ cell harvester (Wallac, Zurich, Switzerland) which transfers the red blood cells onto a glass fiber filter and washes with distilled water. The dried filters are inserted into a plastic foil
- 15 with 10 ml of scintillation fluid and counted in a Betaplate™ liquid scintillation counter (Wallace, Zurich, Switzerland)
- Data are transferred into a graphic programme (e.g. EXCEL), sigmoidal inhibition curves determined and IC<sub>50</sub> values calculated.

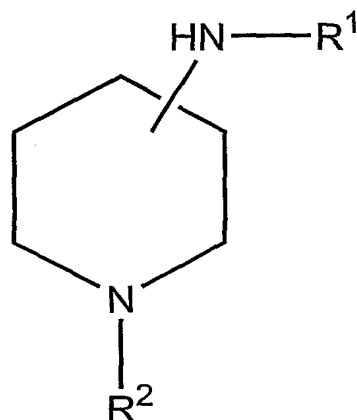
**Table 1:** IC<sub>50</sub> values (nM) for selected compounds:

<b>Example Nr:</b>	<b>IC<sub>50</sub> (nM) on K1</b>
Example 1	770
Example 2	28
Example 3	58
Example 4	28
Example 5	154
Example 6	210
Example 7	246
Example 8	306
Example 9	338
Example 10	266
Example 11	462
Example 12	436
Example 13	540
Example 14	526
Example 15	818
Example 16	672
Example 17	696
Example 18	842
Example 19	244

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The present invention relates to novel, low molecular weight organic compounds of the **general formula I**:



**General Formula I**

wherein

**R¹** represents aryl; heteroaryl; aryl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkyl; heteroaryl-lower alkenyl;

**R²** represents  $-\text{SO}_2-\text{R}^3$ ;  $-\text{CO}-\text{R}^3$ ;  $-\text{CO}-\text{NH}-\text{R}^3$ ;  $-(\text{CH}_2)_p-\text{R}^3$ ; or  $-(\text{CH}_2)_p-\text{CH}(\text{R}^4)_2$  whereby  $\text{R}^4$  may be the same or different;  $-\text{CO}-\text{N}(\text{R}^4)_2$  whereby  $\text{R}^4$  may be the same or different;

**R³** represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; lower alkyl;

**R⁴** represents aryl; heteroaryl; cycloalkyl; lower alkyl;

**p** represents the whole numbers 0, 1, 2, 3, 4 or 5;

and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

In the definitions of the **general formula I** – if not otherwise stated – the expression lower means straight and branched chain groups with one to seven carbon atoms, preferably 1 to 4 carbon atoms which may optionally be substituted with hydroxy or lower alkoxy. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec.-butyl, tert.-butyl, pentyl, hexyl, heptyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-butoxy, sec.-butoxy and tert.-butoxy. Lower alkylendioxy-groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably methylen-dioxy and ethylen-dioxy. Lower alkylen-oxy groups as substituents of aromatic rings onto two adjacent carbon atoms are preferably ethylen-oxy and propylen-oxy. Examples of lower alkanoyl-groups are acetyl, propanoyl and butanoyl. Lower alkenylen means e.g. vinylen, propenylen and butenylen.

The expression **cycloalkyl**, alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl which may be substituted with lower alkyl groups.

The expression **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two heteroatoms chosen from nitrogen, oxygen or sulfur which may be the same or different and which rings may be substituted with lower alkyl, lower alkenyl, aryl, aryl-lower alkyloxy, aryl-oxy, amino, bis-(lower alkyl)-amino, alkanoyl-amino, halogen, nitro, hydroxy, lower alkoxy, phenoxy; examples of such rings are morpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl and substituted derivatives of such type rings with substituents as outlined hereinbefore.

The expression **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzo-fused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom;

five membered aromatic rings containing one oxygen and one nitrogen atom and benzo fused derivatives thereof; five membered aromatic rings containing a sulfur and nitrogen or oxygen atom and benzo fused derivatives thereof; five membered aromatic rings containing three nitrogen atoms and benzo fused derivatives thereof or the tetrazolyl ring; examples of such rings are furanyl, thienyl, pyrrolyl, pyridinyl, indolyl, quinoliny, isoquinoliny, dihydroquinoliny, tetrahydroquinoliny, tetrahydroisoquinoliny, imidazolyl, triazinyl, thiazinyl, pyridazinyl, oxazolyl, whereby such ring systems may be mono-, di- or tri-substituted with aryl, whereby the aryl-rings may again be substituted; aryloxy, aryl-lower alkyl-oxy, lower alkyl; lower alkenyl; lower alkyl-carbonyl; amino; lower alkyl-amino; bis-(lower-alkyl)-amino; lower alkanoyl-amino;  $\omega$ -amino-lower alkyl; halogen; hydroxy; carboxyl; lower alkoxy; vinyloxy; allyloxy;  $\omega$ -hydroxy-lower alkyl; nitro; cyano; amidino; trifluoromethyl; lower alkyl-sulfonyl.

The expression **aryl**, alone or in combination, means six membered aromatic rings and condensed systems like naphthyl or indenyl and the like whereby such ring systems may be mono-, di- or tri-substituted with aryl, whereby the aryl rings may again be substituted, aryloxy, aryl-lower alkyloxy, aryl-lower alkenyl, lower alkyl, lower alkenyl, lower alkyl-carbonyl, aryl-carbonyl, amino, lower alkyl-amino, aryl-amino, bis-(lower-alkyl)-amino, lower alkanoyl-amino,  $\omega$ -amino-lower alkyl, halogen, hydroxy, carboxyl, lower alkoxy, vinyloxy, allyloxy,  $\omega$ -hydroxy-lower alkyl,  $\omega$ -hydroxy-lower alkoxy, nitro, cyano, amidino, trifluoromethyl, lower alkyl-sulfonyl, heteroaryl, whereby the heteroaryl rings may again be substituted.

It is understood that the substituents outlined relative to the expressions cycloalkyl, heterocyclyl, heteroaryl and aryl have been omitted in the definitions of the general formulae I to V and in claims 1 to 5 for clarity reasons but the definitions in formulae I to V and in claims 1 to 5 should be read as if they are included therein.

30

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid; sulfuric acid, phosphoric acid, nitric acid, citric acid, formic acid, acetic acid, maleic acid,

tartaric acid, methylsulfonic acid, p- toluolsulfonic acid and the like or in case the compound of formula I is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

5

The compounds of the general formula I can contain one or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form.

10

The present invention encompasses all these forms. Mixtures may be separated in, a manner known per se, i.e. by column chromatography, thin layer chromatography, HPLC, crystallization etc.

15

The compounds of the general formula I and their pharmaceutically acceptable salts may be used as therapeutics e.g. in form of pharmaceutical compositions. They may especially be used to in prevention or treatment of malaria. These compositions may be administered in enteral or oral form e.g. as tablets, dragees, gelatine capsules, emulsions, solutions or suspensions, in nasal form like sprays or rectally in form of suppositories. These compounds may also be administered in intramuscular, parenteral or intravenous form, e.g. in form of injectable solutions.

20

These pharmaceutical compositions may contain the compounds of formula I as well as their pharmaceutically acceptable salts in combination with inorganic and/or organic excipients which are usual in the pharmaceutical industry like lactose, maize or derivatives thereof, talcum, stearinic acid or salts of these materials.

25

For gelatine capsules vegetable oils, waxes, fats, liquid or half-liquid polyols etc. may be used. For the preparation of solutions and sirups e.g. water, polyols saccharose, glucose etc. are used. Injectables are prepared by using e.g. water, polyols, alcohols, glycerin, vegetable oils, lecithin, liposomes and the like.

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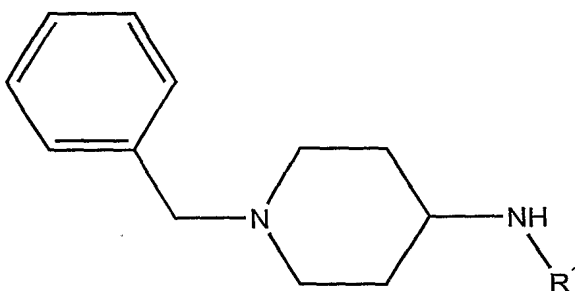
Suppositories are prepared by using natural or hydrogenated oils, waxes, fatty acids (fats), liquid or half-liquid polyols and the like.

5 The compositions may contain in addition preservatives, stability improving substances, viscosity improving or regulating substances, solubility improving substances, sweeteners, dyes, taste improving compounds, salts to change the osmotic pressure, buffer, anti-oxidants and the like.

10 The compounds of formula I may also be used in combination with one or more other therapeutically useful substances e. g. with other antimalarials like quinolines (quinine, chloroquine, amodiaquine, mefloquine, primaquine, tafenoquine), peroxide antimalarials (artemisinin, artemether, artesunate), pyrimethamine-sulfadoxine antimalarials (e.g. Fansidar), hydroxynaphtoquinones (e.g. atovaquone), acroline-type antimalarials (e. g. pyronaridine) and other  
15 antiprotozoal agents like ethylstibamine, hydroxystilbamidine, pentamidine, stilbamidine, quinapyramine, puromycine, propamidine, nifurtimox, melarsoprol, nimorazole, nifuroxime, aminitroazole and the like.

20 The dosage may vary within wide limits but should be adapted to the specific situation. In general the dosage given in oral form should daily be between about 3 mg and about 3 g, preferably between about 10 mg and about 1 g, especially preferred between 5 mg and 300 mg, per adult with a body weight of about 70 kg. The dosage should be administered preferably in 1 to 3 doses per day which are of equal weight. As usual, children should receive lower doses which are  
25 adapted to body weight and age.

Preferred compounds are compounds of the **formula II**



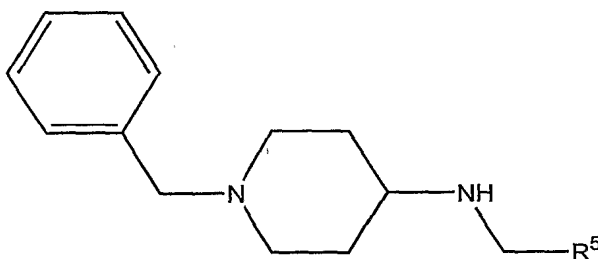
**Formula II**

wherein

5 **R¹** is as defined in general formula I above

and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-  
10 form and pharmaceutically acceptable salts thereof.

Also preferred compounds are compounds of **formula III**



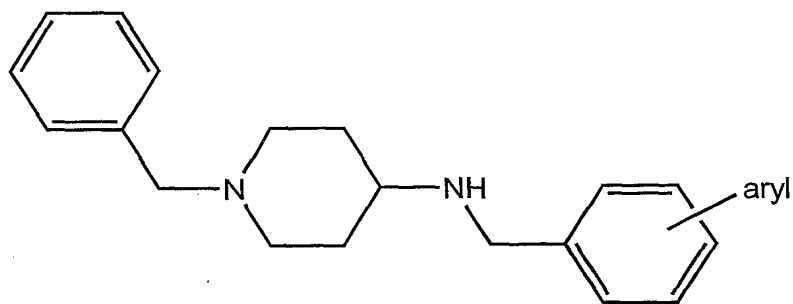
**Formula III**

15 wherein

**R⁵** represents aryl; heteroaryl; cycloalkyl;

and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-  
20 form and pharmaceutically acceptable salts thereof.

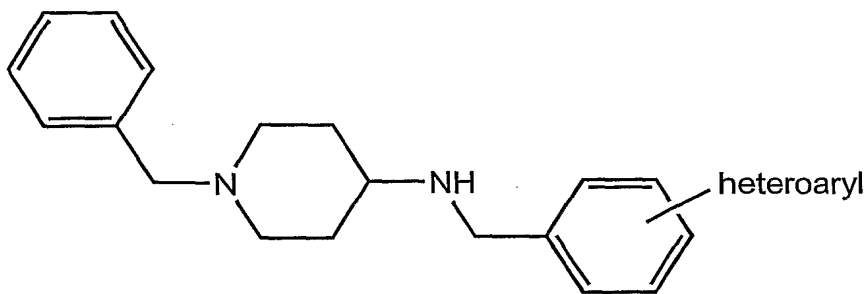
Also preferred compounds are compounds of the **formula IV**



**Formula IV**

5 and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

10 Also preferred compounds are compounds of the **formula V**

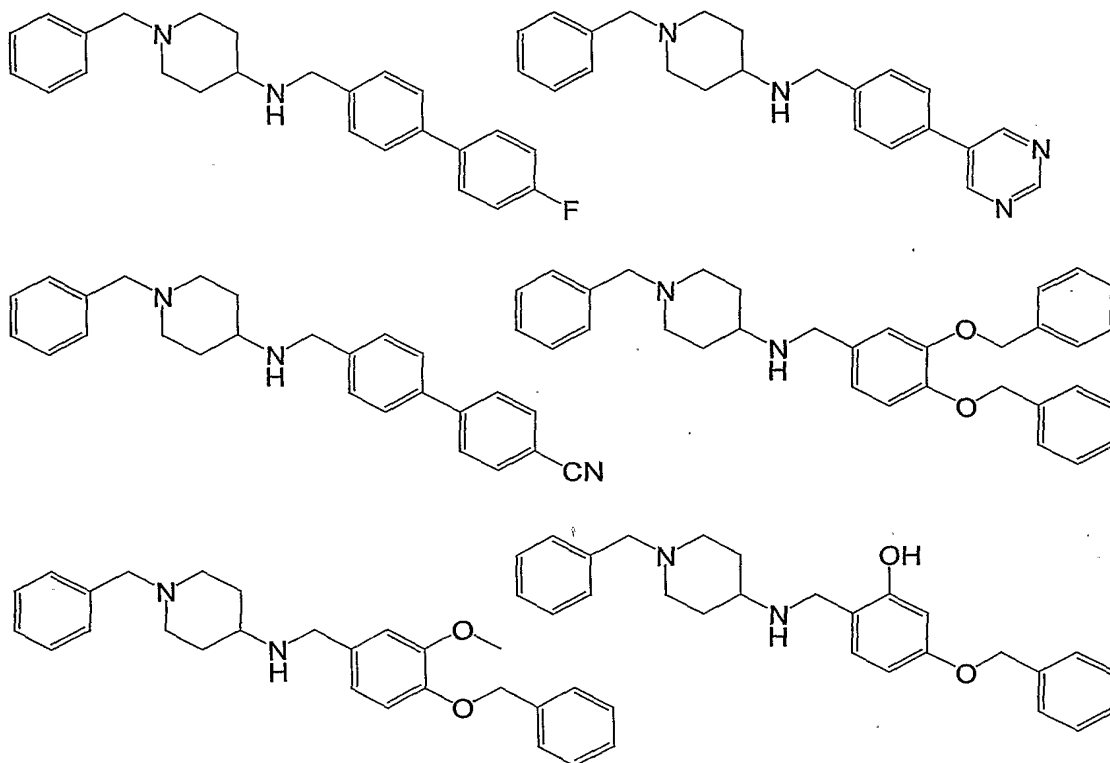


**Formula V**

15 and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

Especially preferred compounds are those depicted in Table 2:

**Table 2:**

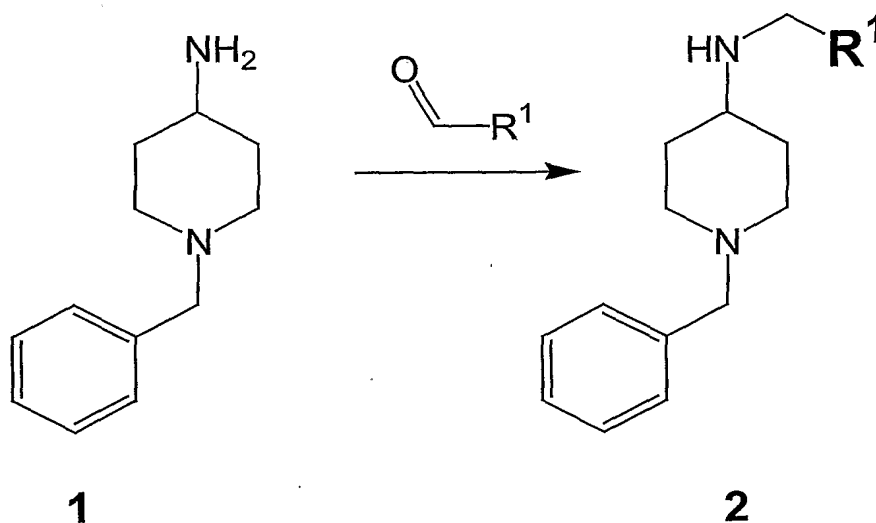


5

The compounds of the **general formula I** of the present invention may be prepared according to the general sequences of reactions outlined below, wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $p$  are as defined in general formula I above (for simplicity and clarity reasons, only parts of the synthetic possibilities which lead to compounds of formulae I to V are described). For general methods of certain steps see also pages 15 – 19 and 20 - 34.

10

Scheme 2: Preparation of substituted 4-amino-N-benzyl-piperidines:



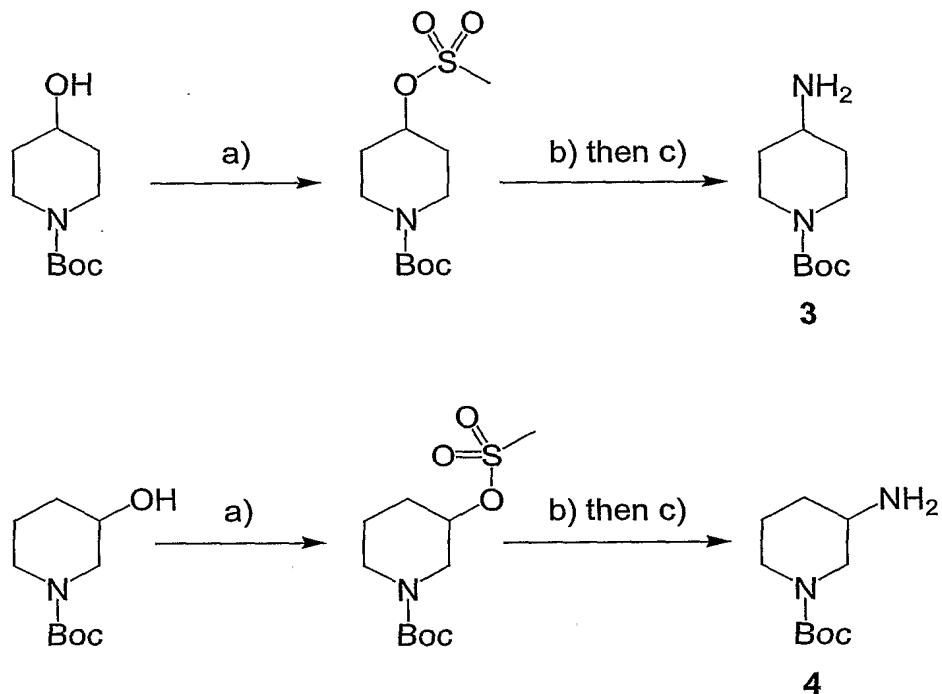
5 Typical procedure for the reductive amination (Synthesis of compounds **2**):

The amine (**1**) and the aldehyde  $\{\text{R}^1\text{-CHO}\}$  (1.5 eq.) are mixed in anhydrous methanol and stirred for 6 h. The mixture is then treated with sodium borohydride (1.5 eq.) and stirred for 2 h. Purified Amberlyst 15 or another suitable scavenger  
 10 is added and the suspension is shaken for 12 h. The resin is then separated by filtration and washed with methanol. The secondary amine **2** is removed from the resin by adding a 2 M methanolic ammonia solution. The resin is drained after 30 min and washed with methanol. The filtrate is evaporated to yield the pure secondary amine **2**.

15

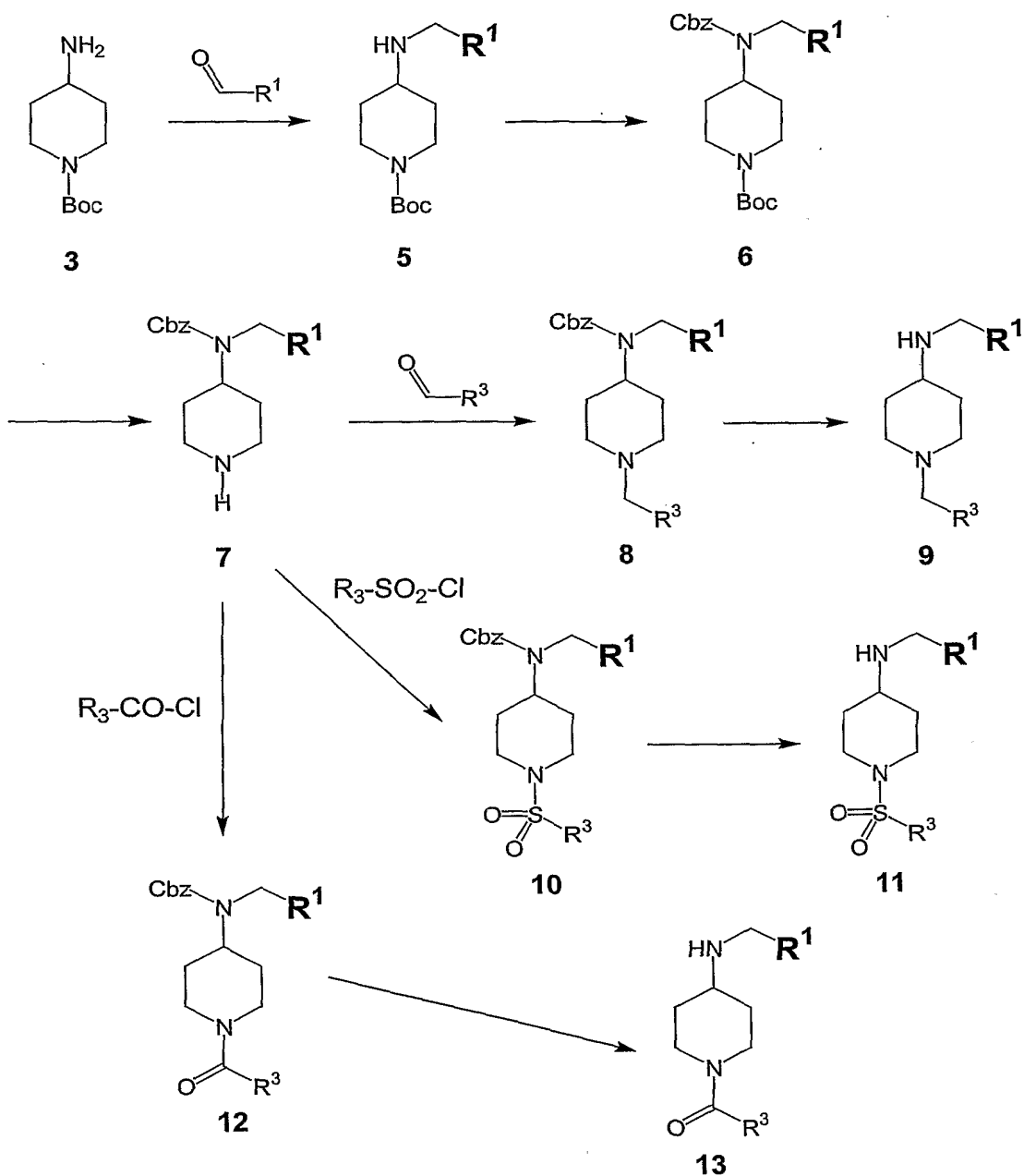
The N-Boc protected 4-amino-piperidine **3** can be prepared in a two step procedure starting by reacting 4-hydroxy-N-Boc-piperidine, with methanesulfonylchloride in an inert solvent like DCM in the presence of a base like TEA to generate 4-mesyloxy-N-Boc-piperidine. The mesyloxy group is  
 20 substituted with sodium azide followed by reduction of the azide functionality to the amino group to give **3**. In accordance to this procedure, the N-Boc protected 3-amino-piperidine **4** can also be prepared in the same way.

Scheme 3: Synthesis of N-Boc-4-aminopiperidine (**3**) and N-Boc-3-aminopiperidine (**4**):



a) Methanesulfonylchloride,  $\text{CH}_2\text{Cl}_2$ ,  $\text{NEt}_3$ , Rt, 12 h; b) Sodium azide, DMF,  $70^\circ\text{C}$ , 6 - 8 h; c) Ethylacetate, Pd/C (10%),  $\text{H}_2$ , reflux, 12 h.

Scheme 4: Preparation of substituted 4-amino-N-(lower alkyl-aryl)-piperidines:



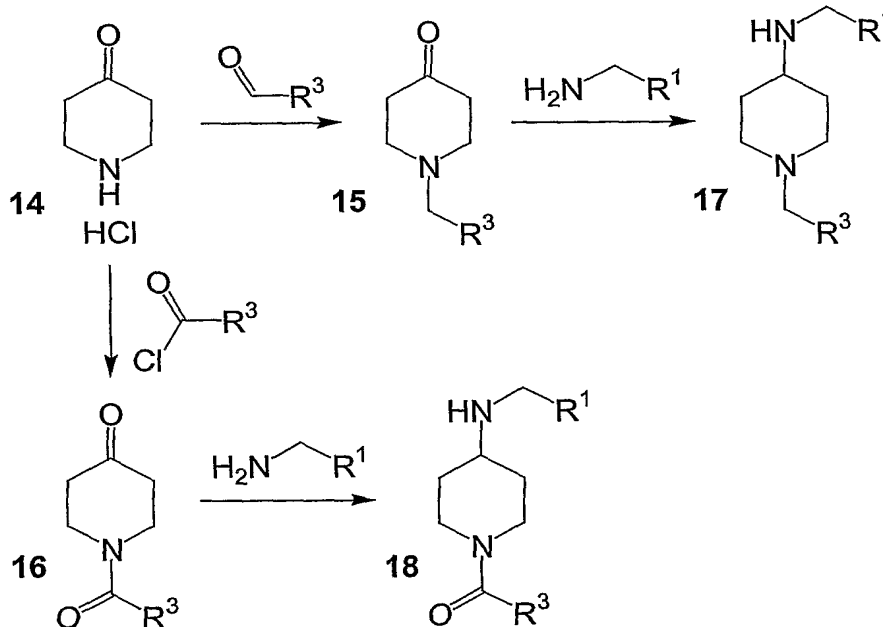
- 5 The amine **3** is transformed to the secondary amine **5** via the typical procedure for the reductive amination described above. Subsequent protection with the Cbz-group to **6** is achieved via typical procedures described in the literature [12-13]. Boc-deprotection is achieved either with hydrochloric acid in a solvent like diethylether or dioxane or with TFA in DCM. The second reductive amination
- 10 step of the intermediate **7** to the compounds **8** again can be performed according

to the typical procedure described above. Compound **7** can also be transformed with acylating reagents like isocyanates, acid chlorides or sulfonyl chlorides to yield products with an urea-, amide- (**12**) or sulfonamide (**10**) functionality instead of the amine functionality at the ring nitrogen atom. Removal of the Cbz-group to form the secondary exocyclic amino functionality (final compounds **9**, **11** and **13**) is performed according to typical procedures described in the literature [12-13].

Compounds based on the 3-amino-piperidine template (see Scheme 3) can be prepared by using 3-amino-N-Boc-piperidine as starting material. All other chemical transformations can be performed as described above in scheme 4.

An equally suitable method for the preparation of compounds according to **general formula I** is depicted in scheme 5 below:

Scheme 5:



Scheme 5 only shows parts of the synthetic possibilities available, starting from piperidine-4-on (14). All chemical transformations can be performed according to procedures published in the literature.

- 5 In general, all chemical transformations can be performed according to well known standard methodologies as described in the literature or as described in the typical procedure above.

10

**The following examples illustrate the invention but do not limit the scope thereof.** All temperatures are stated in °C.

List of abbreviations:

15

Boc or boc	tert.-butoxycarbonyl
Cbz	benzyloxycarbonyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene(1,5-5)
DCM	dichloromethane
20 DMF	dimethylformamide
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
TEA	triethylamine
TFA	trifluoroacetic acid
25 THF	tetrahydrofuran

## General Procedures and Examples:

The following compounds were prepared according to the procedures described for the synthesis of compounds encompassed by the general formulae hereinbefore. All compounds were characterized by <sup>1</sup>H-NMR (300MHz) and  
5 occasionally by <sup>13</sup>C-NMR (75MHz) (Varian Oxford, 300MHz; chemical shifts are given in ppm relative to the solvent used; multiplicities: s = singlet, d = doublet, t = triplet; m = multiplet), by LC-MS (Waters Micromass; ZMD-platform with ESI-probe with Alliance 2790 HT; Colum: 2x30mm, Gromsil ODS4, 3μm, 120A;  
10 Gradient: 0 – 100% acetonitril in water, 6 min, with 0.05% formic acid, flow: 0.45ml/min; t<sub>r</sub> is given in minutes.), by TLC (TLC-plates from Merck, Silica gel 60 F<sub>254</sub>) and occasionally by melting point.

### a) General Procedure:

15

#### *Typical procedure A) for the reductive amination:*

The amine and the aldehyde (1.5 eq.) (which are used as starting materials, are known compounds or the synthesis is described in the relative example), are  
20 mixed in anhydrous methanol and stirred for 6 h. The mixture is then treated with sodium borohydride (1.5 eq.) and stirred for 2 h. Purified Amberlyst 15 or another suitable scavenger is added and the suspension is shaken for 12 h. The resin is then separated by filtration and washed with methanol. The secondary amine is removed from the resin by adding a 2 M methanolic ammonia solution. The resin  
25 is drained after 30 min and washed with methanol. The filtrate is evaporated to yield the pure secondary amine.

*Typical procedure B) for the acylation:*

To a solution of the amine in anhydrous ethyl acetate is added vacuum dried  
5 Amberlyst 21 or another suitable scavenger followed by the addition of the  
carboxylic acid chloride (1.5 eq.). After shaking the suspension for 2 h, an aliquot  
of water is added in order to hydrolyze the excess of the carboxylic acid chloride  
and shaking is continued for 1 h. The resin is then removed by filtration, washed  
with EtOAc and the solution is evaporated to yield the pure amide.

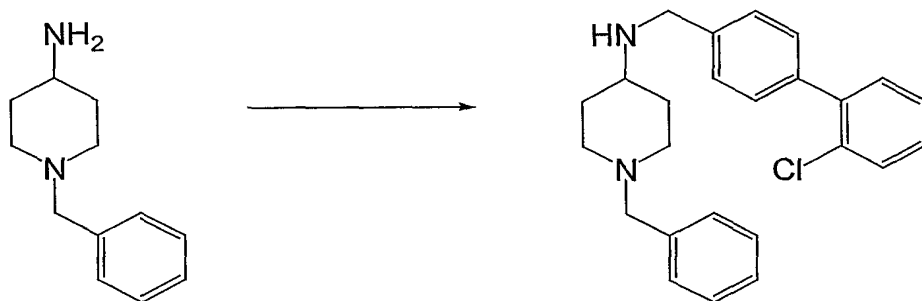
*Typical Procedure C for the reductive amination of a ketone:*

The amine hydrochloride (1 eq) is dissolved in DCM (6 ml / mmol) and TEA (1  
eq) is added, followed by the addition of the ketone (1.5 eq) and sodium  
15 triacetoxo borohydride (1.5 eq) and acetic acid (1 eq). The mixture is stirred for  
12 h. Amberlyst 15 is added and the mixture is shaken for 2 h followed by  
filtration. The resin is washed with methanol and the solvents are evaporated.

**b) Examples:**

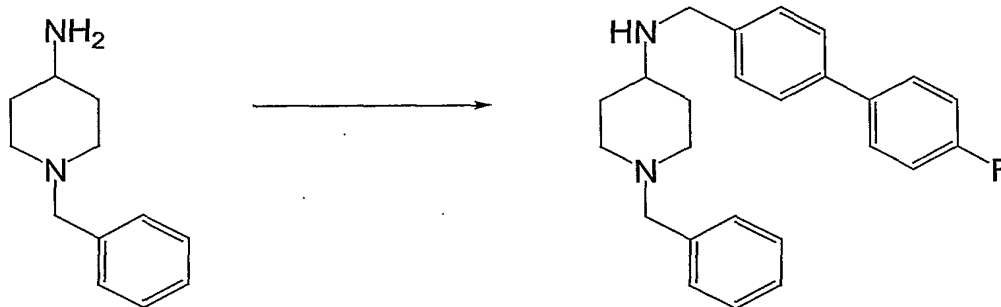
Example 1:

According to typical procedure A), commercially available 1-benzyl-piperidin-4-  
ylamine, is reacted with 2'-chloro-biphenyl-4-carbaldehyde to give (1-benzyl-  
25 piperidin-4-yl)-(2'-chloro-biphenyl-4-ylmethyl)-amine. LC-MS:  $t_R = 3.00$ ; ES+:  
391.24.



## Example 2:

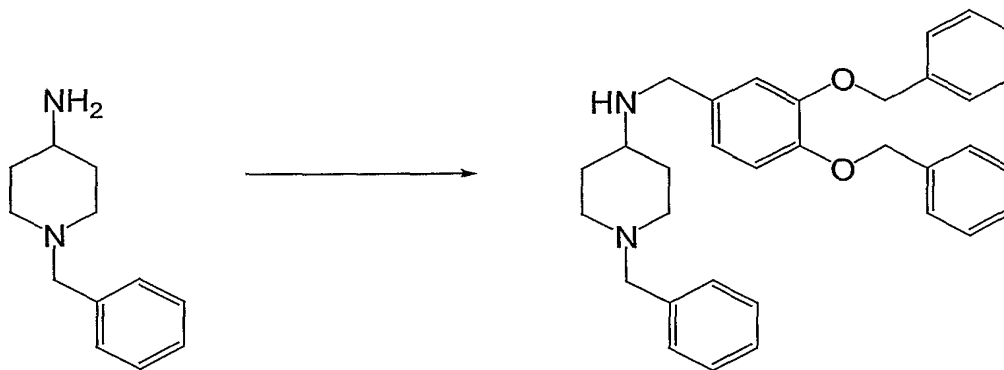
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4'-fluoro-biphenyl-4-carbaldehyde to give (1-benzyl-piperidin-4-yl)-(4'-fluoro-biphenyl-4-ylmethyl)-amine. LC-MS:  $t_R = 2.89$ ; ES+: 375.23.



## Example 3:

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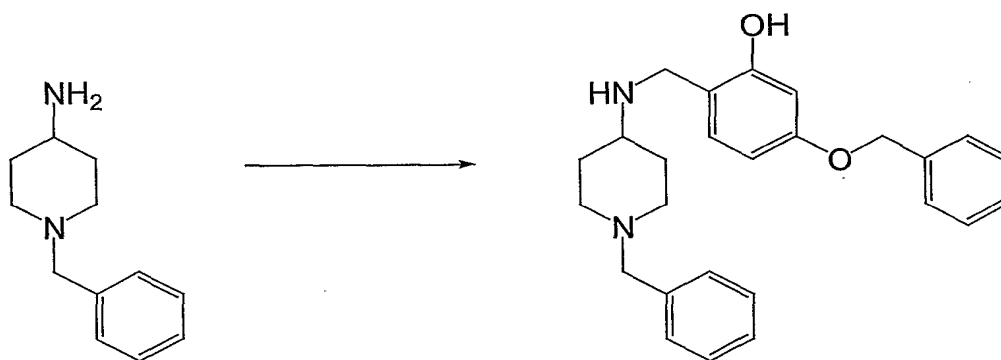
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 3,4-dibenzoyloxy-benzaldehyde to give (1-benzyl-piperidin-4-yl)-(3,4-bis-benzyloxy-benzyl)-amine. LC-MS:  $t_R = 3.44$ ; ES+: 493.52.



15

## Example 4:

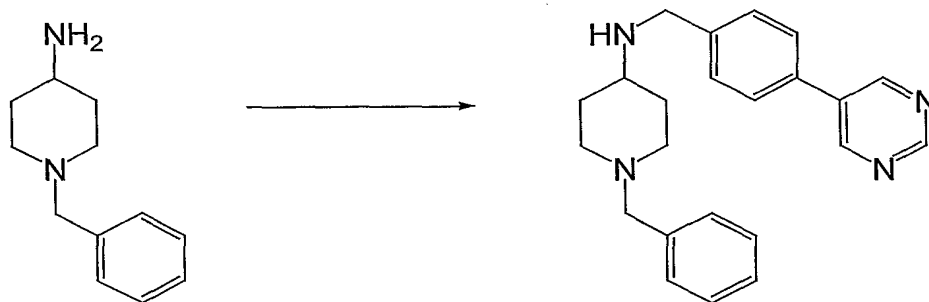
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 2-hydroxy-4-benzyloxy-benzaldehyde to give 5-benzyloxy-2-[(1-benzyl-piperidin-4-ylamino)-methyl]-phenol. LC-MS:  $t_R = 2.80$ ;  
5 ES+: 403.24.



## 10 Example 5:

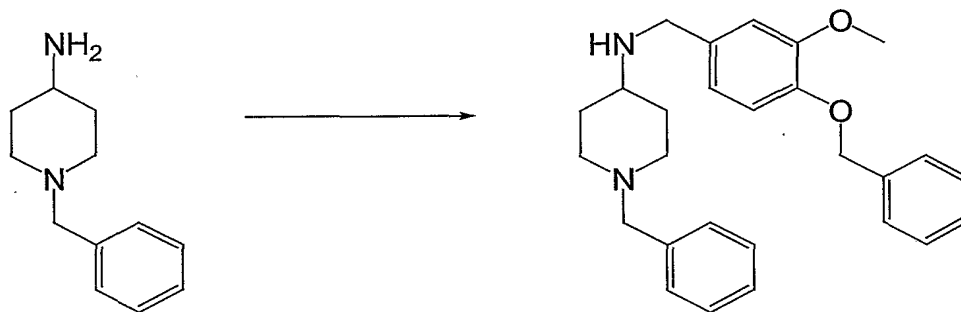
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4-Pyrimidin-5-yl-benzaldehyde to give (1-benzyl-piperidin-4-yl)-(4-pyrimidin-5-yl-benzyl)-amine. LC-MS:  $t_R = 2.34$ ; ES+: 359.27.

15



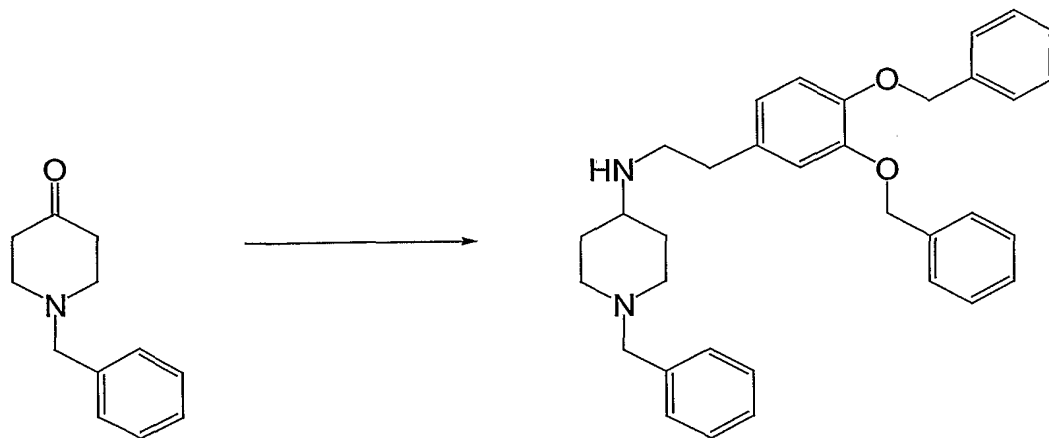
## Example 6:

According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 3-methoxy-4-benzyloxy-benzaldehyde to give (4-benzyloxy-3-methoxy-benzyl)-(1-benzyl-piperidin-4-yl)-amine. LC-MS:  $t_R = 2.81$ ;  
5 ES+: 417.40.



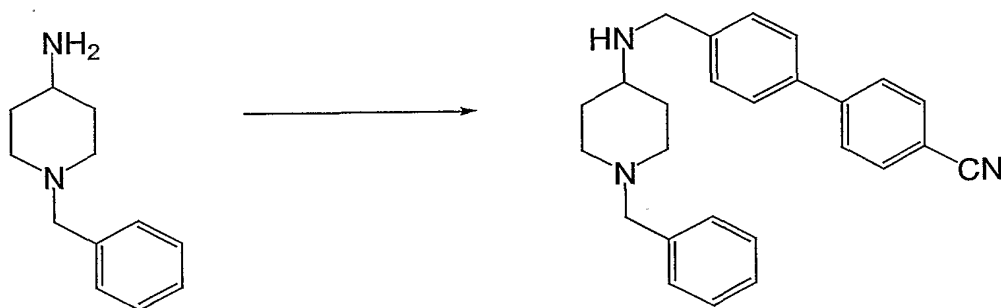
## 10 Example 7:

According to typical procedure C), commercially available 1-benzyl-piperidin-4-one, is reacted with 2-(3,4-bis-benzyloxy-phenyl)-ethylamine to give (1-benzyl-piperidin-4-yl)-[2-(3,4-bis-benzyloxy-phenyl)-ethyl]-amine. LC-MS:  $t_R = 3.44$ ;  
15 ES+: 507.42.



## Example 8:

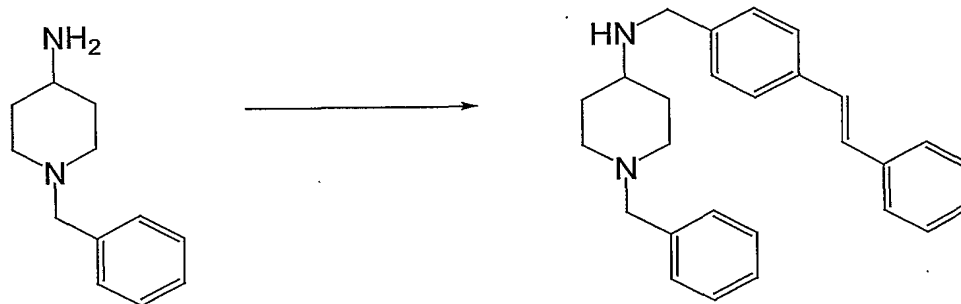
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4'-formyl-biphenyl-4-carbonitrile to give 4'-[(1-benzyl-piperidin-4-ylamino)-methyl]-biphenyl-4-carbonitrile. LC-MS:  $t_R = 2.82$ ; ES+: 382.32.



## 10 Example 9:

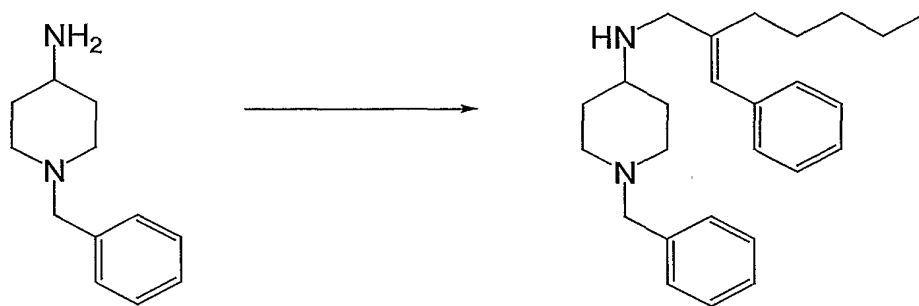
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4-styryl-benzaldehyde to give (1-benzyl-piperidin-4-yl)-(4-styryl-benzyl)-amine. LC-MS:  $t_R = 3.13$ ; ES+: 453.36.

15



## Example 10:

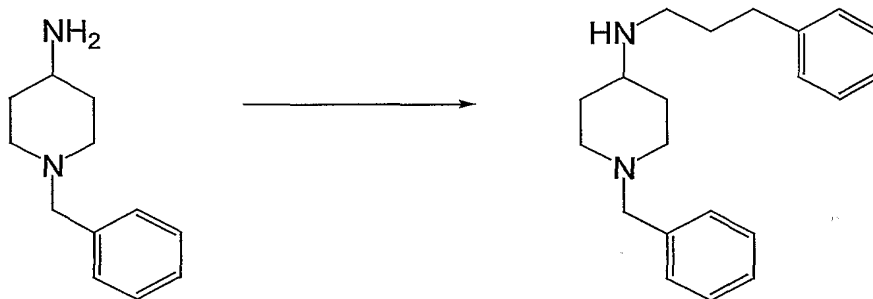
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 2-pentyl-3-phenyl-propenal to give (1-benzyl-piperidin-4-yl)-(2-pentyl-3-phenyl-allyl)-amine. LC-MS:  $t_R = 3.17$ ; ES+: 377.48.



## Example 11:

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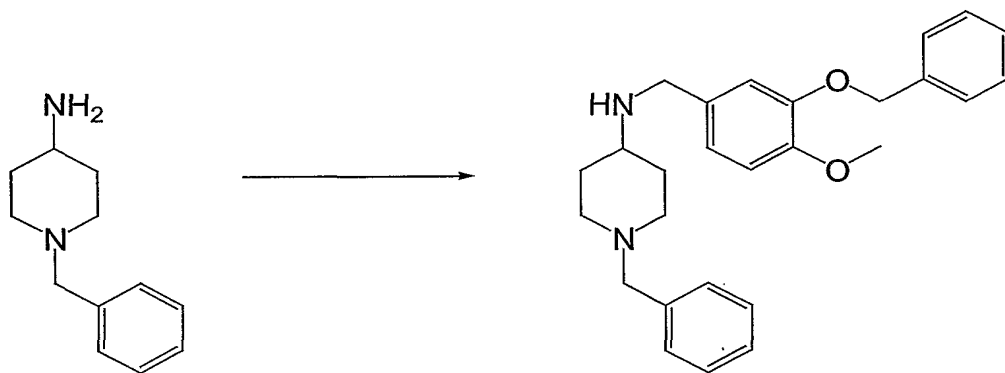
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 3-phenyl-propionaldehyde to give (1-benzyl-piperidin-4-yl)-(3-phenyl-propyl)-amine. LC-MS:  $t_R = 2.34$ ; ES+: 309.35.



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## Example 12:

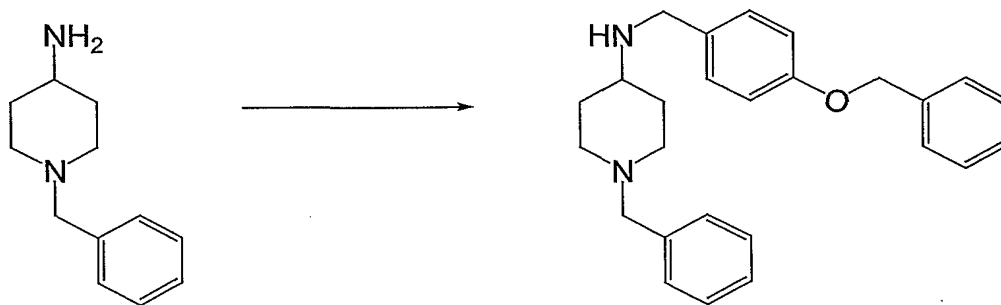
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 3-benzyloxy-4-methoxy-benzaldehyde to give (3-benzyloxy-4-methoxy-benzyl)-(1-benzyl-piperidin-4-yl)-amine. LC-MS:  $t_R = 2.72$ ;  
5 ES+: 417.39.



## 10 Example 13:

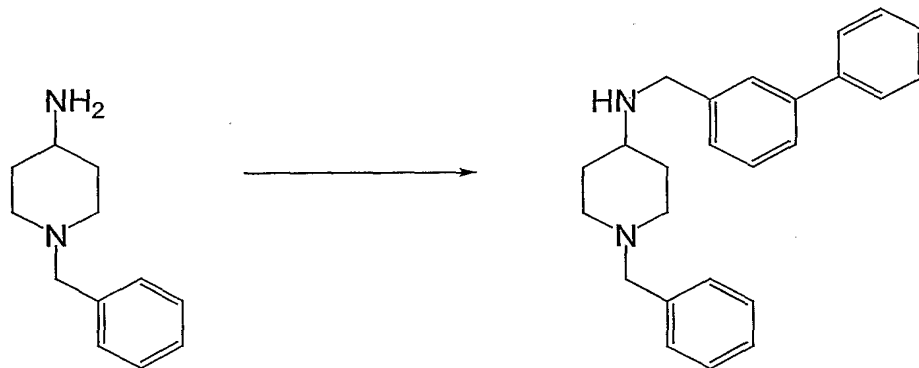
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4-benzyloxy-benzaldehyde to give (4-benzyloxy-benzyl)-(1-benzyl-piperidin-4-yl)-amine. LC-MS:  $t_R = 2.73$ ; ES+: 387.41.

15



## Example 14:

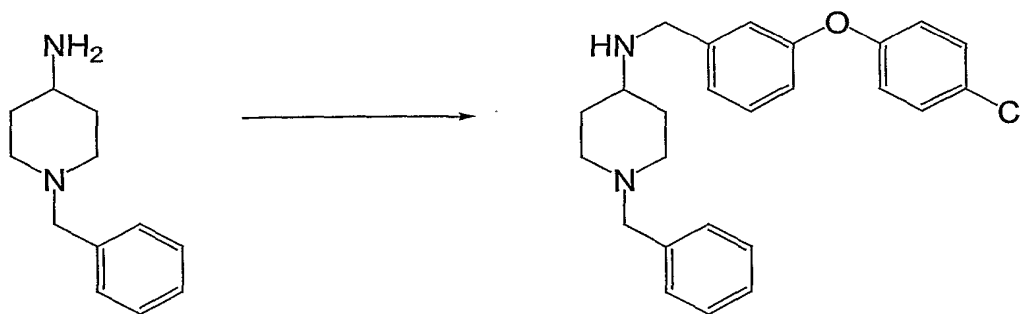
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with biphenyl-3-carbaldehyde to give (1-benzyl-piperidin-4-yl)-biphenyl-3-ylmethyl-amine. LC-MS:  $t_R$  = 2.81; ES+: 357.19.



## Example 15:

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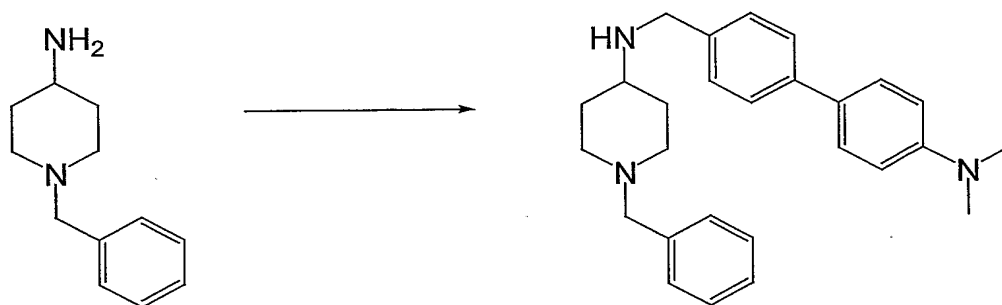
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 3-(4-chloro-phenoxy)-benzaldehyde to give (1-benzyl-piperidin-4-yl)-[3-(4-chloro-phenoxy)-benzyl]-amine. LC-MS:  $t_R$  = 2.86; ES+: 407.37.



15

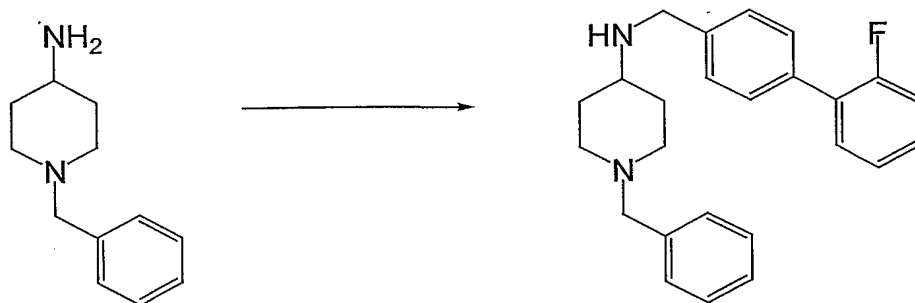
## Example 16:

According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4'-dimethylamino-biphenyl-4-carbaldehyde to give (1-benzyl-piperidin-4-yl)-(4'-dimethylamino-biphenyl-4-ylmethyl)-amine. LC-MS:  $t_R$  = 2.61; ES<sup>+</sup>: 400.30.



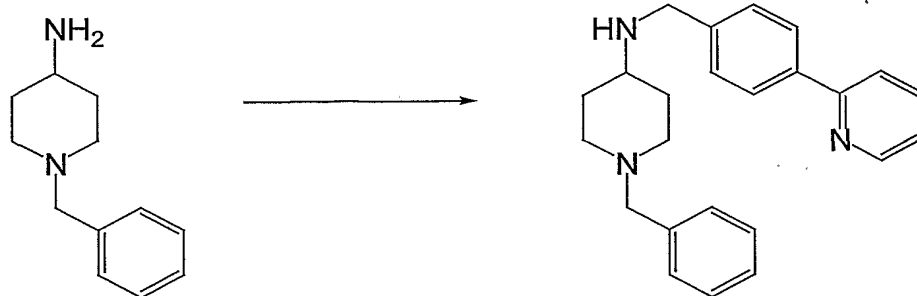
## 10 Example 17:

According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 2'-fluoro-biphenyl-4-carbaldehyde to give (1-benzyl-piperidin-4-yl)-(2'-fluoro-biphenyl-4-ylmethyl)-amine. LC-MS:  $t_R$  = 2.88; ES<sup>+</sup>: 375.29.



## Example 18:

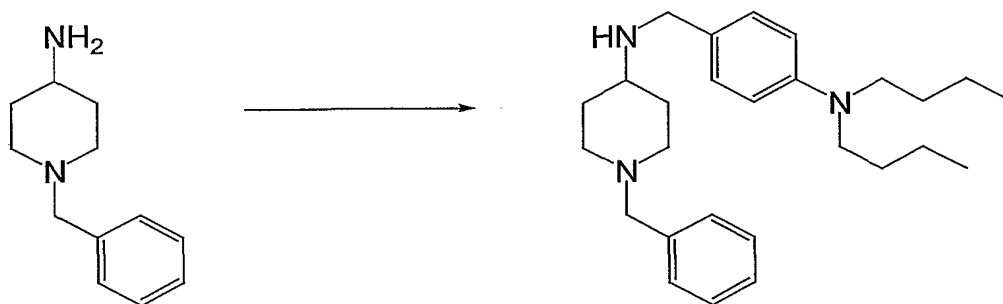
According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4-pyridin-2-yl-benzaldehyde to give (1-benzyl-piperidin-4-yl)-(4-pyridin-2-yl-benzyl)-amine. LC-MS:  $t_R = 2.35$ ; ES+: 358.29.



## Example 19:

10

According to typical procedure A), commercially available 1-benzyl-piperidin-4-ylamine, is reacted with 4-dibutylamino-benzaldehyde to give (1-benzyl-piperidin-4-yl)-(4-dibutylamino-benzyl)-amine. LC-MS:  $t_R = 2.96$ ; ES+: 408.53.



15

Non-commercially available biphenylaldehyde derivatives could be prepared according to the procedure described below:

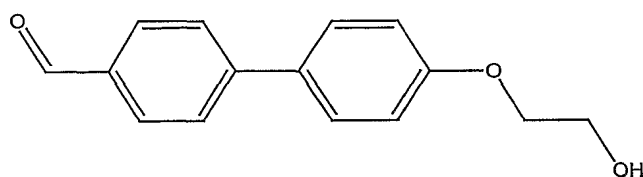
*Typical procedure D) for the Suzuki coupling:*

5

To a solution of an aryl bromide in toluene is added the boronic acid derivative (1.1 eq.) in isopropanol and a 2M aqueous solution of potassium carbonate (5 eq.). The mixture is purged with nitrogen for 10 min and tetrakis(triphenylphosphine) palladium (0.03 eq.) is added. After heating under  
10 reflux for 6 h, water is added to the cooled reaction mixture and the product is extracted with EtOAc. The organic phase is washed with brine and dried over sodium sulfate. The solvent is evaporated to give the crude aldehyde, which is purified by flash chromatography (EtOAc/heptane gradient).

15 Referential Example 1:

According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 2-(4-bromophenoxy) ethanol to give



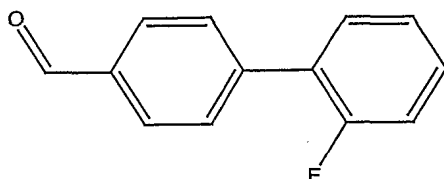
20

4'-(2-Hydroxy-ethoxy)-biphenyl-4-carbaldehyde

## Referential Example 2:

According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-2-fluorobenzene to give

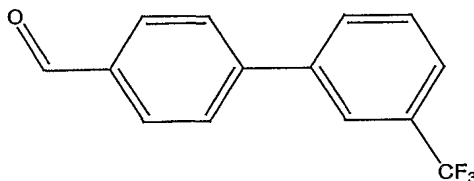
5



2'-Fluoro-biphenyl-4-carbaldehyde

## Referential Example 3:

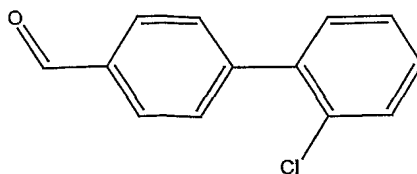
10 According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 3-bromobenzotrifluoride to give



3'-Trifluoromethyl-biphenyl-4-carbaldehyde

## 15 Referential Example 4:

According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-2-chlorobenzene to give



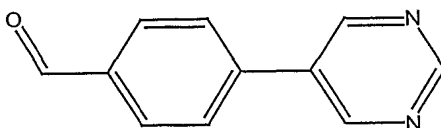
2'-Chloro-biphenyl-4-carbaldehyde

20

## Referential Example 5:

According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 5-bromopyrimidine to give

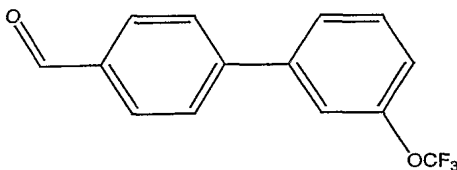
5



4-Pyrimidin-5-yl-benzaldehyde

## Referential Example 6:

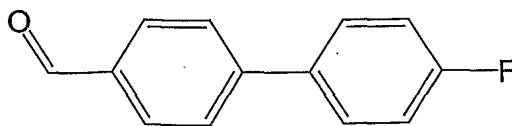
- 10 According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-3-(trifluoromethoxy)benzene to give



3'-Trifluoromethoxy-biphenyl-4-carbaldehyde

- 15 Referential Example 7:

According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 1-bromo-4-fluorobenzene to give



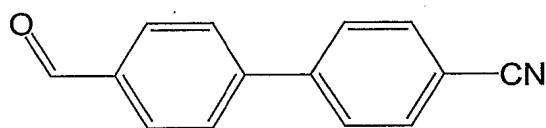
20

4'-fluoro-biphenyl-4-carbaldehyde

## Referential Example 8:

According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 4-bromo-benzonitrile to give

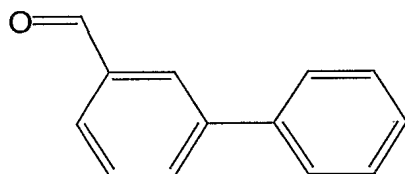
5



4'-formyl-biphenyl-4-carbonitrile

## Referential Example 9:

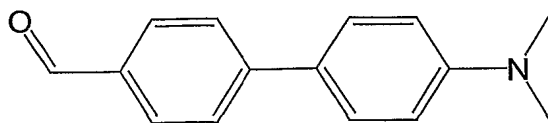
10 According to typical procedure D), 3-formylbenzeneboronic acid is coupled with 4-bromo-benzene to give



Biphenyl-3-carbaldehyde

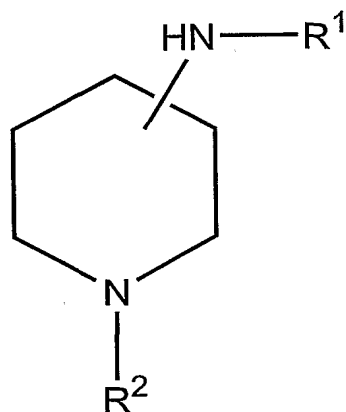
## 15 Referential Example 10:

According to typical procedure D), 4-formylbenzeneboronic acid is coupled with 4-bromo-N,N-dimethylaminobenzene to give



20

4'-dimethylamino-biphenyl-4-carbaldehyde

**Claims:**1. Compounds of the **general formula I****General Formula I**

wherein

**R¹** represents aryl; heteroaryl; aryl-lower alkyl; aryl-lower alkenyl; heteroaryl-lower alkyl; heteroaryl-lower alkenyl;

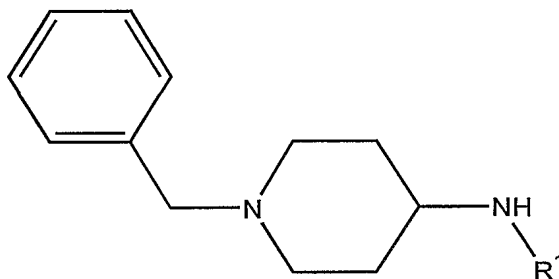
**R²** represents —SO<sub>2</sub>-R<sup>3</sup>; —CO-R<sup>3</sup>; —CO-NH-R<sup>3</sup>; —(CH<sub>2</sub>)<sub>p</sub>-R<sup>3</sup>; or —(CH<sub>2</sub>)<sub>p</sub>-CH(R<sup>4</sup>)<sub>2</sub> whereby R<sup>4</sup> may be the same or different; —CO-N(R<sup>4</sup>)<sub>2</sub> whereby R<sup>4</sup> may be the same or different;

**R³** represents aryl; aryl-lower alkyl; heteroaryl; heteroaryl-lower alkyl; lower alkyl;

**R⁴** represents aryl; heteroaryl; cycloalkyl; lower alkyl;

**p** represents the whole numbers 0, 1, 2, 3, 4 or 5;

and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

2. Compounds of **formula II****Formula II**

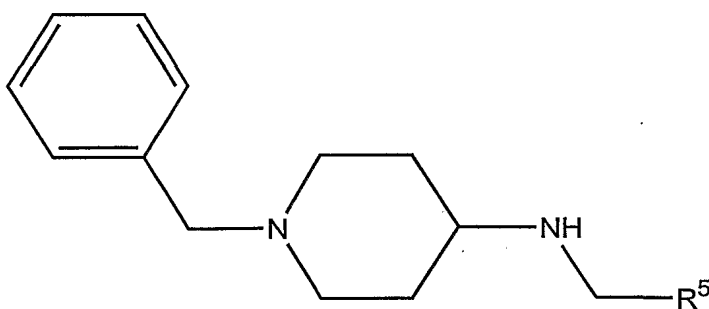
5 wherein

**R¹** is as defined in general formula I above

and optically pure enantiomers, mixtures of enantiomers such as for example  
10 racemates, optically pure diastereomers, mixtures of diastereomers,  
diastereomeric racemates, mixtures of diastereomeric racemates and the meso-  
form and pharmaceutically acceptable salts thereof.

3. Compounds of **formula III**

15

**Formula III**

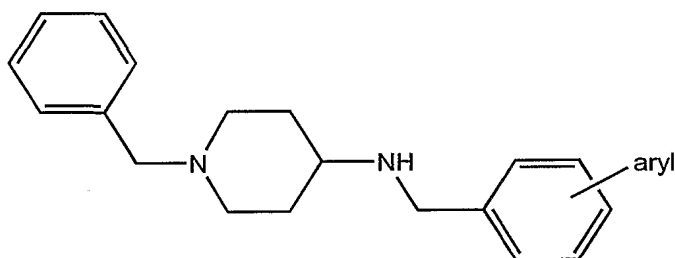
wherein

**R⁵** represents aryl; heteroaryl; cycloalkyl;

and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

5

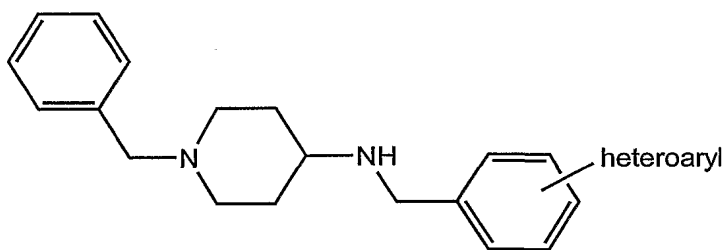
#### 4. Compounds of **formula IV**



**Formula IV**

10 and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

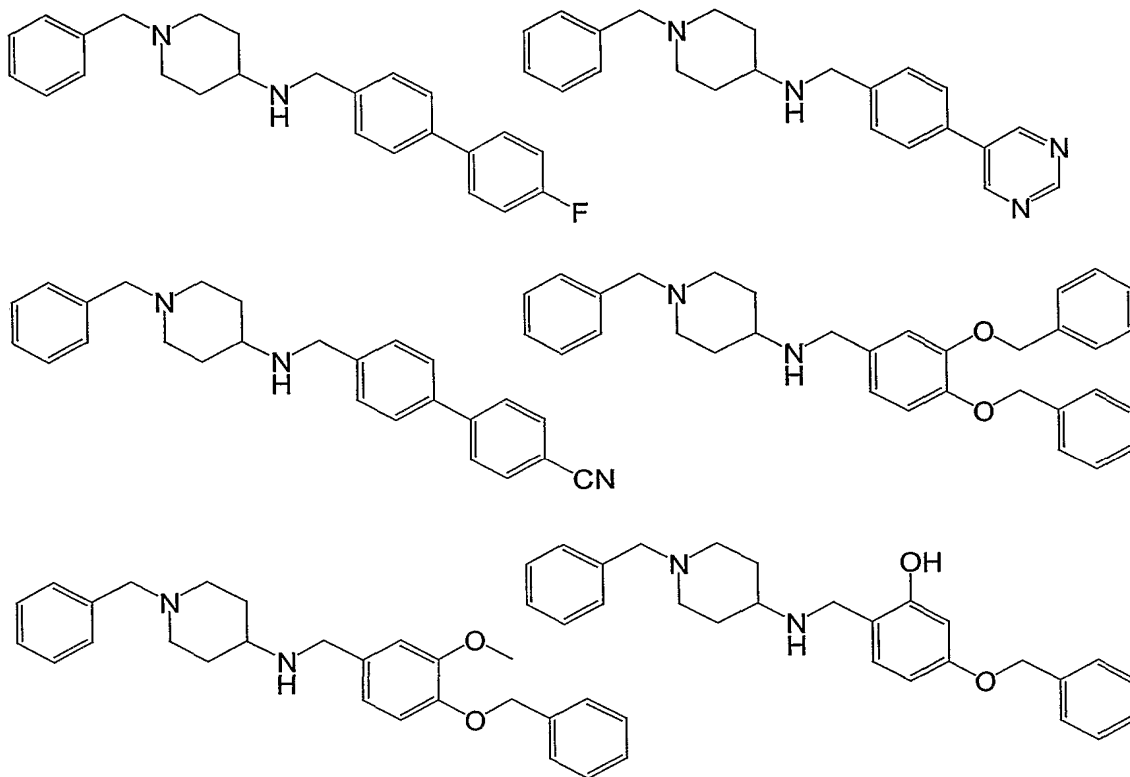
#### 15 5. Compounds of **formula V**



**Formula V**

20 and optically pure enantiomers, mixtures of enantiomers such as for example racemates, optically pure diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates and the meso-form and pharmaceutically acceptable salts thereof.

6. A compound according to any one of the claims 1 to 5, having a structure selected from the group consisting of:



5

7. A compound as described as end-product in any of the examples 1 to 19.

8. Pharmaceutical compositions containing one or more compounds as claimed in any one of claims 1 to 7 and inert excipients.

10

9. Pharmaceutical compositions according to claim 8 for treatment or prevention of diseases demanding the inhibition of protozoal enzymes like serine-, cysteine- or aspartyl- or metalloproteases or digestive enzymes and combinations thereof.

15

10. Pharmaceutical compositions according to claim 8 for treatment or prevention of diseases demanding the interruption of the reproductive cycle of a protozoa.

11. Pharmaceutical compositions according to claim 8 for treatment or prevention of malaria.

12. Pharmaceutical compositions according to claim 8 for treatment or  
5 prevention of protozoal infections.

13. Pharmaceutical compositions according to claim 8, which contain aside of one or more compounds of the general formula I at least one known HIV protease inhibitor or at least one known HIV reverse transcriptase inhibitor or at  
10 least one known antimalarial agent or at least one known antiprotozoal agent or at least one known cathepsin D or E inhibitor or combinations thereof.

14. A process for the preparation of a pharmaceutical composition according to any one of claims 8 to 13, characterized by mixing one or more active  
15 ingredients according to any one of claims 1 to 7 with inert excipients in a manner known per se.

15. Use of at least one of the compounds of the general formula I for the treatment or prevention of diseases by administering the compound in a suitable  
20 method and formulation and in a therapeutically effective dose to cure protozoal infections.